The forces of cancer

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A tumour is a dysfunctional cellular community. Not only does mutation lead to uncontrolled proliferation, radical shape changes, and identity crises in cancer cells - many other cell types are corrupted by the bad influence of the tumour, engaging in malicious behaviours that aid tumour cells directly and disrupt normal organ functions. The actions of multiple cell types in a tumour eventually make their own environment uninhabitable, leading to a toxic sprawl that spreads throughout the tissue and ultimately the body. In some cases, cancer cells – with the assist of other cell types such as cancer associated fibroblasts (CAFs) – can leave the primary tumour and start the process anew in distant tissues. Despite all we know about cancer, a number of key questions remain to be answered, not least about the role of the physical microenvironment. How do the various cell types in a tumour make sense of their surroundings, in particular by transmitting mechanical information from the external matrix into nuclei? How do cancer cells communicate with each other over long distances within and between tissues? And how do tumours promote the wide-ranging structural remodelling seen in primary tissues and metastatic sites?

The theme of the "Forces In Cancer" Hooke Meeting held over two sunny days during 2018 in London, was how information is propagated within cells and between cell occurs via mechanical forces. Cells in and around tumours are constantly being pushed, pulled, pressed, and squeezed, both by other cells and by the extracellular matrix (ECM). The constant demolition and reconstruction of the ECM by cancer cells and others, such as tumour-associated macrophages and CAFs, represents a particular mode of information transmission, where cells change their environment as a way to direct the behaviour of other cells.

In this special issue, speakers at this meeting have contributed reviews from their unique perspectives, opinion pieces, and original research centred on the role of mechanical forces in tumourigenesis and metastasis.

Cellular organelles as mechanotransducers

Keith Burridge, a pioneer in the field of mechanobiology, discusses mechanotransduction on the cellular scale, specifically how cell surface receptors transmit signals to the nucleus via mechanical tension and Rho GTPases (Burridge et al, this issue). Critical to this information propagation paradigm is the concept of the nucleus itself as a semi-rigid mechanoresponsive element. Pere Rocha-Cosachs and colleagues discuss the plasma membrane as a mechanochemical transducer, illustrating how the lipid bilayer and its protein components respond and adapt to tensile and shear stresses (Le Roux et al, this issue).

Influences of mechanical forces of the dynamics of cellular processes

Cells not only sense mechanical forces, but respond by altering cancer-relevant behaviours such as proliferation, differentiation, inflammation, and drug resistance. Martin Humphries and colleagues discuss how force sensing regulates progression through the cell cycle, providing mechanistic insights that explain how proliferation of tumours is driven by increased ECM stiffness (Jones et al, this issue). Similarly, Sasha Bershadsky and colleagues provide novel experimental insights into how myosin II and plasma membrane tension modulate podosome dynamics (Rafiq et al, this issue).

Tumour cell migration in mechanically complex environments

Cancer cell migration was a recurring theme in the "Forces in Cancer" symposium because the engagement of migratory programmes underpins tumour metastasis. This themed issue tackles the subject of tumour cell motility in a number of different contexts. Benny Geiger and colleagues contribute new research showing how cross-talk between the stroma and tumor cells promotes tumour cell migration via synergistic effects of cytokines (Elisha et al, this issue). Giorgio Scita and colleagues provide a thought-provoking piece discussing whether migration is indeed a selectable trait that occurs during tumour evolution (Disanza et al, this issue). Because tumour cell migration in the body occurs in complex 3D environments with diverse mechanical and geometric properties, developing new model systems that mimic these environments is an important challenge for cancer biology research. Jan Lammerding and Noam Zuela-Sopilniak review the state-of-the-art in these systems (Zuela-Sopilniak and Lammerding, this issue), and Katrina Wolf and colleagues provide original research showing how the morphological alterations that occur during 3D migration underpin migratory speed and acceleration (Krause et al, this issue). Notably, cell migration in 3D depends strongly on the mechanical properties of the nucleus, underscoring its importance as a mechanotransducing element.

Bioengineering approaches in tumour mechanobiology

Cancer mechanobiology research is an inherently and increasingly multidisciplinary endeavour. From hydrogels, to microfluidic devices, to complex organ-on-chip platforms, the last decade has witnessed an explosion of new materials and devices that have been engineered to more closely recapitulate features of the tumour microenvironment for fundamental research, diagnostic, and drug discovery applications. However, a challenge to working with these models is quantifying both the phenotypes themselves, as well as different parameters of the systems itself (i.e. hydrogel stiffness). In this issue, Val Weaver and colleagues survey current methods for quantifying ECM and cell mechanics at different scales, with a particular focus on brain and CNS tumours (Ayad et al, this issue). Shelley Peyton and colleagues discuss new metrics for assessing the response of cancer cells in hydrogel and co-culture matrices to small-molecule treatments from an engineering perspective (Brooks et al, this issue). The utility and challenges of mathematical modelling in cancer biology are also recurring themes throughout this issue.

Leveraging cancer mechanobiology to develop new therapeutics

The ultimate goal of tumour biology research is to devise new ways to cure and prevent cancer. Given the current excitement regarding immune modulators as cancer therapeutics, it is no surprise that interplay of cell-cell and cell-ECM mechanical cross-talk was a hot topic of the meeting. The ECM plays a complex role in immune cell modulation, and as such represents a potential avenue for engaging the body's own defence mechanisms against tumours, but also a new set of challenges for immunotherapy. In this issue, Sophie Acton and colleagues review literature on how the ECM both can impede and promote immune cell infiltration and activation in solid tumours (Martinez et al, this issue). Dennis Discher and colleagues posit that the softness of cancer cells could allow them to evade engulfment by macrophages, and discuss how blocking CD47 could circumvent this mechanical barrier (Andrechak et al, this issue).

Conclusion

While this issues highlights both the recent progress that has been made in cancer mechanobiology, and points to the future, the authors also address some intellectual and technology challenges that must be overcome in order to get better understanding of forces in cancer. Perhaps foremost amongst these is the development of research models that better mimic the complex nature of tumours – both in terms of cellular diversity, complex geometry, and dynamic mechanics. But importantly, such models must allow analytics on the single cell level; especially quantitative imaging approaches. We believe that continued discussion between bioengineers, physicists, imaging specialists and cancer biologists is thus essential is driving the field of tumor mechanobiology forward, and most opportunities for establishing collaborations between these fields should exist.

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Authors' contributions

All authors contributed actively to the writing of the paper and have approved the final version of the manuscript.

Competing interests

We declare we have no competing interests.

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